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(54) Title of the Invention : Thiazolidine derivative

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(22) Date of application : 24/8/1987

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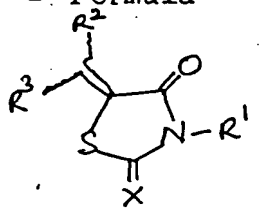
S p e c i f i c a t i o n s

1. Title of the Invention : Thiazolidine derivative.

2. Scope of the Invention :

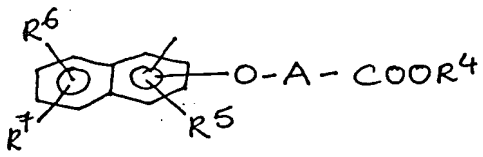
(1) This invention deals with thiazolidine derivative and its salts which are represented by the following formula (1)

- Formula - (1)

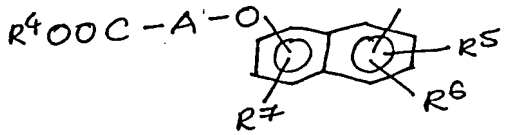


(In which, R_1 represents hydrogen atom, amino group which may be substituted by acyl and C_1 - 15 alkyl which may be substituted by low grade alkoxy carbonyl or carboxyl, R_2 represents hydrogen atom or low grade alkyl; x represents sulphur atom or oxygen atom; whereas R_3 represents the groups as specified at the formula (a) (b), (c) or (d) given below

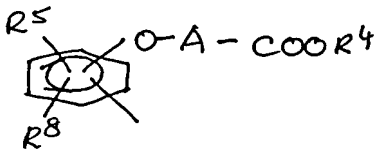
- Formula (a) -



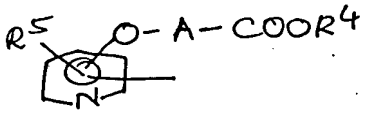
- Formula (b) -



- Formula (c)



- Formula (d) -



In these formulae, R_4 represents hydrogen atom, low grade alkyl or aralkyl $R_5 \sim R_8$ represent the same or different hydrogen atom, hydroxy, halogen atom low grade alkyl, low grade alkoxy, nitrite, trifluoromethyl or amino; A represents low grade alylene or low grade alkenylene; X represents sulphur atom R_5 and R_8 both represent hydrogen atom If R_4 represents hydrogen atom, etnyl or carboxy methyl A represents low grade alkylene above C_2 or low grade alkenylene above C_3.

3. Details of the Invention :

Industrial Applications

This invention deals with thiazolidine derivative and its salts which discnarge the function of impeding/inhibiting aldose retardase (Hereinafter referred to as HR)

Old Methods:

As per Bull 500 chim. Belg. 72, 87~90 (1962) the compounds similar to the compound specified as per this invention, can be obtained with a view to use it for anti microbrial activity and growth adjustment. But it hardly mentions that this compounds discharge the function of impeding/inhibiting AR.

The patents such as Tokkaisho 57-28074, 57-40478, 60-136575, 60-156387, 61-27984, 61-53271, 61-56175 etc. deal with the compounds possessing the activity of AR impedence.

The Compound as per this invention totally differs in the Structure the Compounds recommended as per the above patents as it consists of carboxy low grade alkoxy on the aromatic ring as the substituent.

Details of the Invention:

AR is the enzyme which reduces aldoses such as glucose, glactose etc. into polyoles such as sorbitol, glactitde etc. in vivo. On the other hand, it is well-known that to the visceral organs and the tissues such as sorbitol, glactidole ~~etc~~ etc. which are produced by means of AR take an active part in causing/promoting the symptoms of diabetes (diabetic cataract, diabetic retino pathia, nervous break down etc)

The compound which is recommended as per this invention, possesses the function of inhibiting/impeding AR. In this way, it proves effective in preventing and curing the diabetic symptoms.

~~This~~ This invention deals with thiezolidine derivative and its salts which are represented as per formula (I) below

- Formula (I) -

(In which R_1 represents hydrogen atom, C1 - 15 alkyl which may be substituted by low grade alkoxy x carbonyl or carboxyl or amino group which may be substitued by acyl; R_2 represents hydrogen atom or low grade alkyl; X represents sulphur atom or oxygen atom; R_3 represents the groups specified as per formulae (a), (b), (c) or (d) below.

Formula (a)

Formula (b)

Formula (c)

Formula (d)

In this case, R_4 represents hydrogen atom, low grade alkyl or aralkyl; $R_5 \sim R_8$ represent the same or different hydrogen atom, hydroxy, halogen atom, low grade alkyl, low grade alkoxy, nitrite, trifluoro methyl or amino; A represents low grade alkylene or low grade alkenylene ; R_5 and R_8 both represent hydrogen atom; If 'R' represents hydrogen atom, ethyl or carboxy methyl, A represents low grade alkylene above C_2 or low grade alkenylene above C_3)

As per these specifications, alkyl, alkoxy, alkylene and alkenylene may be allowed to ~~be~~ of straight chain or branched chain.

When it comes to low grade alkyl, it shall include methoxy ethoxy, propoxine, iso propoxy etc. with carbon No. ranging from $1 \sim 6$.

As for low grade alkylene, it shall include methylene, ethylene, trimethylene, tetamethylene, pentamethylene, hexamethylen heptamethylene etc. having carbon no. in a range of $1 \sim 10$.

When it comes to low grade alkenylene, it shall include 2-propynylene, 2-butenylene, 3-methyl-2-butenylene, 3-methyl-2-butenylene, 3-or 4-pentenylane, 2-, 3-, 4- or 5-hexanylene etc. having carbon no. in a range of $3 \sim 6$ consisting of double bond beyond the position between $1 \sim 2$.

Acyl represents aliphatic or aromatic carboxylic acid residual group consisting of carbon no. ranging from $1 \sim 7$, such as formyl, acetyl, propionyl, butyryl, benzoyl etc.

As ~~RRR~~ for aralkyl, it includes benzyl, phenetyl, napthyl methyl etc. with carbon atom no. ranging from $1 \sim 4$, substituted with aromatic ring.

When it comes to halogen atom, it represents fluorine, chlorine, bromine, iodine etc. Out of these, fluorine, chlorine and bromine are more preferrable.

As for the salts of compound (I) which are recommended as per this invention, it is allowed to use non poisonous salts which are physiologically permissible, such as the salts of organic bases and inorganic bases like salts of ethyl amine, salts of ammonium, salts of calcium, salts of potassium, salts of sodium etc.

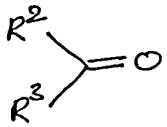
As for the compound (I) and its salts which are recommended as per this invention, they are likely to be present in the form of hydrates or solvants, this invention includes these hydrates as well as solvents.

Since the compound (I) which is recommended as per this invention is likely to consist of one or more carbon-carbon double bond or one or more assymetric carbon atom as the case may be , it contains stereoismer accordingly. This invention also includes these stereoisomers and their mixtures.

Compound (I) which is recommended as per this invention can be manufactured by implemnting the methods (a) and (b) as given below.

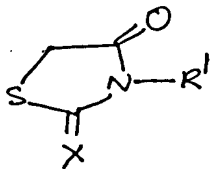
(a) The compounds specified at formulae (II) and (III)

Formula (II)



(In which R_2 and R_3 are the same as above)

Formula (III)



(In which R, and X are the same as above)

react with each other so as to obtain compound (I) as recommended by this invention. This reaction is, normally, promoted in a suitable solvent. As for the suitable solvents, it is allowed to use alcohols such as methanol,

ethanol, isopropyl alcohol or acetic acid, water and aromatic hydrocarbons such as dimethyl formamide, chloroform, pyrridine, cyclohexane and benzene, toluene, xylene etc. These solvents can be used in single form or mixed up.

It is advisable to promote reaction in the presence of alkoxides of alkaline metals, inorganic bases or organic bases. As for organic bases, it is allowed to use sodium acetate, potassium acetate, ammonium acetate, piperidine acetate, piperidine benzoate, salts of diethyl amine organic acids etc. When it comes to alkoxides of alkaline metals, it is allowed to use sodium methoxide, sodium ethoxide, potassium t-butoxide etc. In case of inorganic bases, it is recommended to use potassium hydroxide, sodium hydroxide, sodium carbonate, potassium carbonate etc. When it comes to organic bases, it is advisable to use thiethyl amine, morpholine, piperidine, 1, 8 - diazabicyclo (5,4,0) undeca-5-en(Hereinafter referred to as DBU), 1,5 - diazabicyclo (4.3.0) nonane -5- en(Hereinafter referred to as DBN) It is also allowed to add acetic anhydride or zinc chloride to the above said bases or salts depending on the case, When it comes to the reaction temperature, it is advisable to maintain it in a range of $0^{o}c \sim 200^{o}C$ or preferrably in a range of $0^{o}c \sim 120^{o}c$.

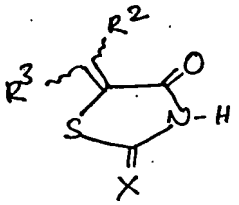
As per formula (I) the compound in whose case, R_4 represents hydrogen atom is likely to be obtained in the form of free carboxylic acid or its salts as per the post treatment conditions after the reaction. Free carboxylic acid or its corresponding salts can be treated with acids so as to obtain the desired compound.

As for the compound as per formula (I) in whose case R_4 represents hydrogen atom, the compound in whose case R_4 represents low grade alkyl or aralkyl is obtained by promoting hydrolysis in respect of sodium bicarbonate or potassium bicarbonate in the solution mixed up with water and alcohols such as ethanol, methanol etc. or the solution mixed up with water and cyclicesters

such as dioxane, tetrahydrofuran etc. or the solution obtained by mixing them up, in the presence of catalyst.

As per formula (I) the compound (in whose case R_4 represents low grade alkyl group) can be obtained by heating the compound (in whose case R_4 represents hydrogen atom) and its corresponding alcohols at room temperature or applied themperature in the presence of acid ~~a~~ catalyst or without the presence of catalyst.

(b) In case R_1 represents C_{1-15} alkyl which may be substituted with low grade alkoxy carbonyl, reaction takes place between compound which is represented as per formula (IV) below:-



- formula (IV) -

(In which R_2 and R_3 represent the same as above) and the compound which is represented as per formula (V) below:-

- Formula (V) -

$$R^1-Y$$

(In which R_1 represents C_{1-15} alkyl which may be substituted with low grade alkoxy carboxyl; y represents halogen atom)

So as to obtain the compound which is recommended as per this invention at formula (I). It is advisable to promote this reaction in the alcohol solvents such as methanol, ethanol, propanol etc, and dimethyl formamide (hereinafter referred to as DMF) and in the presence of acid catalysts such as sodium hydride, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydroxide, potassium hydroxide, DBU, DBN etc.

The compound (I) which is manufactured as above can be changed into the salt as specified above through ordinary method.

The compound (I) or its salts as recommended by this invention, can be can be separated and purified by carrying out the methods such as extraction enrichment, neutralization, filtration, re-crystallization, column chromatography, high speed liquid chromatography or ion exchange resin etc.

The compound at (I) or its salts discharge the function of impeding/inhibiting AR and bringing down, the blood sugar effectively. It also proves effective in preventing/curing diabetic symptoms.

Let us now deal with the pharmocological/aspepts of this invention.

Test : AR impeding/inhibiting activity.

This test conforms to S. Highman and J.H. Kinoshita method (J. Biochem. 242 877∼882 1965))

(Prepration of raw/crude enzyme solution).

Firstly homogenize the rock crystal substance (which is extracted from whister type rat) with 5 M phosphoric acid buffer solution (PH 7.4, 1 mM mercaptoethanol containing). Later carry out centrifugal separation of 18,000 X g for 20 minutes. Further, promote salting out by adding solid type, ammonium Sulphate to it so as to ensure that 40 ∼ 75% saturated ammonium sulphate demarcation/separated portion becomes raw (crude) enzyme solution.

(Measurement of enzymatic activity): Take the solution containing 0.08 M Phosphoric acid buffer solution, 0.47 M Lithium Sulphate, 1.76×10^{-4} M NADPH and 1.76×10^{-3} glycer aldehyde (PH 6.2, 1.7 ml). To this, add the solution containing the compound (for testing purpose) at various types of concentration (o.2 ml). Ensure incubation at 30^{o} c and then add crude enzyme solution (0.1 ml) so as to initiate the reaction. After adding the enzyme solution,

measure the absorbance at 340 nm with the help of double beam spectrophotometer (150-20 model) of Hitachimake. Now, enzymatic activity can be determined from the decrease in the absorbance.

Table - 1.

Test Compound	IC_{50}(M)	Test Compound	IC_{50} (M)
1*	1.3×10^{-3}	49	1.8×10
2	1.4×10^{-3}	50	2.1×10^{-3}
3	1.7×10^{-3}	51	1.6×10^{-3}
4	1.1×10^{-3}	52	1.8×10^{-3}
5	3.3×10^{-3}	53	3.5×10^{-3}
9	2.8×10^{-3}	54	4.4×10^{-3}
11	1.5×10^{-3}	56	4.1×10^{-3}
12	1.8×10^{-3}	63	1.9×10^{-3}
15	3.7×10^{-3}	64	3.8×10^{-3}
34	4.2×10^{-3}	66	3.9×10^{-3}
39	2.4×10^{-3}	68	4.9×10^{-3}
40	4.2×10^{-3}	70	3.1×10^{-3}
45	3.7×10^{-3}	73	3.5×10^{-3}
47	2.8×10^{-3}	74	3.1×10^{-3}
48	2.9×10^{-3}	Quelcetin	5.2×10^{-3}

* It represents the compound at experiment 1 (same is applied for the compounds below)

As for the administration of this compound (I) and its physiologically permissible salts, it is allowed to administer them orally, non-orally, into the rectum or into the eyes. As for its dosage, it depends mostly on the type of the compound, way of administration, condition of the patient and his age etc, But generally, it is advised to administer it at a dosage ranging from 0.1 mg~10 mg/kg/day. It is allowed to use the compound (I) and its salts in the form of formulation obtained by mixing it up with the carrier (support) for formulation. When it comes to the carrier for formulation, it is recommended to use such substances which are normally used in the formulation and which do not react with compound (I) and its salts. In this regard, it is allowed to use milk sugar, grape sugar, mannit, dextrin, cyclo dextrin, starch, white sugar, magnesium aluminic metasilicate, aluminium synthetic silicate, crystalline cellulose, carboxy methyl cellulose calcium ION exchange resin, methyl cellulose, gelatin, gum arabic, hydroxy propyl cellulose, hydroxy propyl cellulose of low substitutivity, hydroxy propyl methyl cellulose, poly vinyl pyrrolidone, poly vinyl alcohol, light silicic anhydride, magnesium stearate, talc, tragacanth, bentonite, bee gum, carboxy vinyl polymer, titanium oxide, sorbitane fatty acid esters, sodium lauric sulphate, cacaobutter, glycerin (glyceral), esters of fatty acid glyceral, pure lanoline, glycero gelatin, poly sorbate, macrosole, vegetable oil, wax, propylene glycol, water etc. As for the medicine, it is allowed to take it in the form of tablets, capsules, syrup, suspension, injection, granules, eye drops etc. When it comes to liquied formulation it is allowed to suspend or dissolve it in water or other suitable mediums. It is also suggested to ensure coating as per ordinary methods in case of tablets, granules etc.

As for such formulations, it is allowed to maintain compound (I) or its physiologically permissible salts at 0.5% minimum or preferrably in a range of 1~70%. It is also allowed to use

6ther ingredients which prove effective in the treatment.

Let us now deal with this invention with the help of a few references and experiments. However, it is not compulsary to restrict this invention to these experiments only.

Reference 1 :

After dissolving metallic sodium (2.4 gms) in 4-(1-formyl-2-napthyl oxy) butyric ethyl ethanol (200ml), add 2-hydroxy napthaldehyde (17.2 gms) and then carryout reflex for a period of one hour. After eliminating ethanol, dissolve the residue in dry DMF (110ml) and add 4-ethyl bromo butyrate (21.5gms). Then carryout stirring on heating it at 60°C for a period of 4 hours. Enrich the reaction solution under vaccum pressure and dissolve the residue in chloroform. Later carryout acid base treatment as per ordinary method so as to obtain 8.8gms of desired substance in the form of oil.

Reference 2 4 :

Use corresponding hydroxy benzaldehyde derivative or hydroxy napthaldehyde derivative in place of 2-hydroxy napthaldehyde and perform the rest of the process in the same way as specified at reference 1 so as to obtain the following compounds.

Reference 2 : 4-(2-formyl-4-chloro-phenoxy) ethyl butyrate.

Reference 3 : 4-(2-formyl-4-bromophenoxy) ethyl butyrate.

Reference 4 : 4-(1-formyl-6, 7-dimethoxy-2-napthyloxy) ethyl butyrate.

Reference 5 :

(5-bromo-1-formyl-6-methoxy-2-napthyloxy) methyl acetate.

After dissolving metallic sodium (0.44 gms) in ethanol (100ml), add 5-bromo-2-hydroxy-6-methoxy-1- napthaldehyde (4.9 gms) and apply heat to it. Later eliminate ethanol. Add dimethyl

formamide (100 ml) and α-methyl bromo acetate (2.2 ml) and stirr it at 80°C for a period of 17 hours. After cooling it, add the reaction solution to ice water and carryout extraction with toluene. After washing it with water, dry it with Glauber's salt and then concentrate it under vaccum pressure. Recrystallize the residue from ethanol so as to obtain 4.2 gms of the desired product M.P 154-157°c.

Reference 6 9 :

Use corresponding hydroxy benzaldehyde derivative or hydroxy napthaldehyde derivative in place of 5-bromo-2-hydroxy-6-methoxy-1-napthaldehyde which is used in reference 5. Perform the rest of the process in the same way as specified at Reference 5 so as to obtain the following compounds.

Reference 6 : (2-bromo-4-formyl-6-methoxy phenoxy) methyl acetate

Reference 7 : (2-chloro-4-formyl-6-methoxy phenoxy) methyl acetate.

Reference 8 : (4-chloro-2-formyl-1-napthyloxy) methyl acetate.

Reference 9 : (1-formyl-6, 7-dimethoxy-2-napthyloxy) methyl acetate.

Reference 10 : (2-(1-formyl-2-napthyloxy) ethyl butyrate.

Use 2-ethyl bromo butyrate in place of 4-ethyl bromo butyrate which is used in reference 1, so as to obtain the desired compound in the form of Oily substance.
Mas spectrum m/Z : 286 (M+).

Reference 11 :

4-(4-formyl-2-methoxy phenoxy) ethyl chrotonate.

Carryout the reaction in respect of 4-hydroxy-3- methoxy benzaldehyde and 4-ethyl bromo chrotonate in the same way as specified at Reference 1 so as to obtain the desired product in the form of oily substance.

Mass spectrum m/Z : 264 (MT)

Reference 12 : 4-(1-formyl-2-napthyloxy) butyric acid.

Carryout heat reflux for a period of one hour in respect of 4-(1-formyl-2-napthyloxy) ethyl butyrate (8gms) in the mixed solution containing water (30ml) with sodium hydroxide (1.5gms)-ethanol(40ml). After carrying out post treatment in accordance with ordinary method, recrystallize it from water so as to obtain 5.5 gms of desired product. mp 179-181°c.

Reference 13~20 :

Promote the reaction byusing the corresponding ester compounds in place of 4-(1-formyl-2-napthyloxy) ethyl butyrate (which is used at Reference 12) in the same way as specified at Reference 12 so as to obtain the compounds specified below.

Reference 13 : 2-bromo-4-formyl-6-methoxy
Phenoxy acetic acid mp 118~120°c.

Reference 14 : 2-chloro-4-formyl-6-methoxy phenoxy
Acetic acid mp 118~121°c.

Reference 15 : 4-(4-chloro-2-formyl phenoxy)
Butyric acid mp 95~96°c.

Reference 16 : 4-(4-bromo-2-formyl phenoxy)
Butyric acid mp 100~103°c

Reference 17 : 1-formyl-2-napthyloxy
Acetic acid mp 176~179°c

Reference 18 : 4-chloro-2-formyl-1-napthyloxy
Acetic acid mp 180~182°c

Reference 19 : 5-Bromo-1-formyl-6-methoxy-2-napthyloxy
Acetic acid mp 224~228°c

Reference 20 : 1-formyl-6, 7-dimethoxy-2-napthyloxy
Acetic Acid mp 213~219°c

Reference 21 :

2-formyl-5-methoxy carbonyl methoxy pyridine.

Dissolve 3-hydroxy-6-hydroxy methyl pyridine (4gms) in the solution containing sodium ethoxide (metallic sodium 1.15 gms; ethanol 100ml) which is prepared for the purpose. After carrying out heat reflux for one hour, eliminate ethanol through distillation. After dissolving the residue in dimethyl formamide (80ml), add methyl bromo acetate, carry out heating at 80°c for 3 hours. Later eliminate dimethyl formamide. Carryout extraction of the residue with ethylacetate. Then dry it with Glauber's salt and concentrate it so as to obtain oily substance. Purify it with silica get column chromato (Developed solvent, chloroform-methanol). so as to obtain 2-hydroxy methyl-5-methoxy carbonyl methoxy pyridine (1.8gms). Dissolve this product (0.85 gms) in chloroform (40ml), add manganese dioxide (2.4gms) and carryout heating reflux for a period of 3 hours so as to obtain the sediment. Eliminate it through filtration wash it with chloroform and then dry the filtered solution with Glouber's salt. Later concentrate it so as to obtain the desired compound (0.63gms). mp 50~55°c

Reference 22 :

4-OXO-2-thioxo thiazolidine-3-undecanic acid.

Add the water solution (500ml) containing potassium hydroxide (85%, 19.8gms) under ice cooling, to the water solution (90ml) containing 11-amino undecanic acid (30.1gms). Then stirr it at room temperature for a period of 1.5 hours. Add carbon dioxide (10ml) to it and stirr it at room temperature for a period of 0.5 hours. Then wash it with ether: Further add the water solution (120ml) containing potassium carbonate (20.7gms) and mono chloro acetic acid (14.6gms) which is prepared separately, to this water layer. Keep it overnight under room temperature. Make it acidic with dilute Hydrochloric acid and stirr it under room temperature for a period of one hour. Filter the sediment and stirr it in 6N Hydrochloric acid at 100°c for a period of 3 hours. Ensure ice cooling and filter the sediment thus deposited; dissolve it ethyl acetate and add n-hexane. Felterout the crystals thus

deposited. Concentrate the filtered liquid and carryout recrystallization repeatedly from acetic ethyl-n-hexane so as to obtain 16.7gms of the desired product. mp 72-74°c.

Experiment 1 :

5-(3-carboxy methoxy-4-methoxy benzyledene)-4-OXO-2-thioxo thiazolidine-3-acetic acid.

Dissolve 4-OXO-2-thioxo thiazolidine-3-acetic acid (0.70gms) 3-formyl-6-methoxy phenoxy acetic acid (0.78gms) and sodium acetic anhydride (0.61gms) in ice acetic acid (12ml). Heat and stirr it at 110°c for 48 hours. After cooling eliminate ice acetic acid. Add dilute hydrochloric acid to the residue and stir it for one hour. After filtering the sediment, wash it with water, recrystallize it from water contained ethanol so as to obtain 0.2gms of the desired compound. mp 250°c minimum.

Experiment 2 :

5-(2-(3-carboxy propoxy) benzyledene)-4-oxo-2-thioxothiazolidine 3-acetic monosodium salt.

Dissolve 4-OXO-2-thioxothiazolidine-3-acetic acid (0.48gms), 4-(2-formyl-phenoxy) butyric acid (0.52gms) and sodium acetic anhydride (0.41gms) in ice acetic acid (10ml); carryout heating and stirring at 100°c for a period of 56 hours. After cooling, eliminate ice acetic acid. Wash the residue with water and recrystallize it from methonol so as to obtain the desired product (0.45gms). mp 250°c minimum.

Experiment 3 :

5-(3-bromo-6-carboxy methoxy benzyledene)-4-OXO-2-thioxo thiazyledene.

Dissolve 4-OXO-2-thioxo thiazolidine (0.42gms)-4-bromo-2-formylphenoxy acetic acid (0.80gms) and sodium acetic anhydride (0.51gms) in ice acetic acid (15ml); carryout heating and reflux

for a period of 4~5 hours. After cooling, add water and stirr it for one hour. Filter the sediment and add dilute hydrochloric acid to it. After stirring it for one hour, filter the sediment and process it with active carbon. Later recrystallize it from the solution containing acetone water so as to obtain 0.46gms of desired product. mp 252 - 254°c.

Experiment 4 :

5-(2-carboxy methoxy-1-napthyl methylene)-3-methyl-4-oxo-2-thioxo thiazolidine.

Dissolve 1 formyl-2-napthoxy acetic acid (4.72gms), 3-methyl-4-oxo-2-thioxo thiazolidine (3.2gms) and sodium acetic anhydride (3.28gms) in acetic acid (50ml), carryout heating and reflux for 4 hours. Flter the deposited sediment so as to obtain crude crystals to which add dilute hydrochloric acid. Stirr it for one hour and filter the crystals. Then carry out active carbon process and recrystallize it from acetone-water so as to obtain 4.3gms of desired product. mp 206 - 209°c.

Experiment 5~96 :

Use corresponding compounds as the raw materials and perform these experiments in the same way as specified at experiment 1 so as to obtain the following compounds.

Experiment 5 :

5-(2-carboxy methoxy-1-napthyl methylene)-4-oxo-2-thioxo thiazolidine.

(mp 231~234°c/recrystallizing solvent : acetic acid-water).

Experiment 6 :

5-(2-carboxy methoxy-1-napthyl methylene)-4-oxo-2-thioxo thiazolidine-3-acetic acid.

(Mass spectrum m/Z :403 (MT))

Experiment 7 :

5-(1-carboxy methoxy-4-chloro-2-napthyl methylene)-4-oxo-2-thioxo-thiazolidine.

(mp 250°c minimum/recrystallizing solvent : acetone-water)

Experiment 8 :

5-(1-carboxymethoxy-4-chloro-2-napthyl methylene)-3-methyl-4-oxo-2-thioxo-thiazolidine.

(mp 224~226°c/recrystallizing solvent : acetone -water)

Experiment 9 :

5-(1-carboxy methoxy-4-chloro-2-napthyl methylene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 250°c mimimum/recrystallizing solvent : Acetonitrile-water).

Experiment 10:

5-(4-chloro-1-methoxy carbonyl methoxy-2-napthyl methylene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 181~183°c/recrystallizing solvent : ethanol - water).

Experiment 11 :

5-(5-bromo-2-carboxy methoxy-6-methoxy-1-napthyl methylene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 215~220°c/recrystalizing solvent : Acetone - water)

Experiment - 12

5 - (5-Bromo - 2- Carboxy methoxy - 6 - Methoxy - 1 - napthyl methylene)- 4 - 0x0 - 2 - Thioxo thiazolidine - 3 - Acetic Acid
(mp 135~143°C / recrystallizing solvent: Acetone - Water)

Experiment - 13

5 - (6 -(3 - Ethoxy carbonyl propoxy) - 2 - hydroxy - 1 - napthyl methylene) - 3 - methyl - 4 - oxo - 2 - thioxo thiazolidine
(mp 137~142°C / recrystallizing solvent: chloroform - n - hexane)

Experiment - 14

5 - (2 - (3-ethoxy carbonyl propoxy) - 6 - hydroxy - 1 - napthyl methylene)- 3 - methyl - 4 - oxo - 2 - thioxo thiazolidine.
(mp 124~129°C / recrystallizing solvent: Chloroform - n - hexane)

Experiment - 15

5 - (2-(3 - Carboxy propoxy) - 1 - napthyl - methylene) - 4 - oxo - 2 - thioxo thiazolidine - 3 - acetic acid.
(mp 159~161°C / recrystallizing sovlent: ethylacetate - n-hexane)

Experiment - 16

5 -(2-(3 - carboxy propoxy) - 1 - napthyl methylene) - 3 - methyl - 4 - oxo - 2 - thioxy thiazolidine.
(mp 93~95°C / recrystallizing solvent: ethyl Acetate - n-hexane).

Experiment - 17

5 - (2- (2-Carboxy - 1 - methylethoxy) - 1 - napthyl methylene) - 3 - methyl - 4 - oxo - 2 - thio thiazolidine.
(mp 157~164°C / recrystallizing solvent: Acctone - Water).

Experiment - 18.

5 - (6 - bromo-2 - Carboxy methoxy - 1 - napthyl methylene) - 4 - oxo - 2 - thipxo thiazolidine - 3 - Acetic Acid.
(Mass spectrum m/z : 481, 483 (M^+)).

Experiment - 19

5 - (6 - bromo - 2 - (3-carboxy propoxy - 1 - napthyl methylene) - 4 - oxo - 2 - thioxo thiazolidine.

(mp 181~188°C / recrystallizing solvent: Acetone - Water)

Experiment - 20

5 - (6 - bromo - 2- (3-carboxy propoxy - 1 - napthyl methylene) - 3- methyl - 4 - oxo - 2- thioxo thiazolidine.

(mp 100~103°C / recrystallizing solvent: Acetone - Water)

Experiment - 21

5 - (6 - bromo - 2 - (3-carboxy propoxy - 1- napthyl methylene) -4-oxo-2-thioxo thiazolidine - 3 - Acetic Acid.

(mp 129~134°C / recrystallizing solvent: Acetone - Water)

Experiment - 22

5 - (2-(2 - carboxy ethoxy) - 1 - napthyl methylene) - 4 - oxo - 2 - thioxo thiazolidine.

(mp 175~185°C / recrystallizing solvent: Acetone - Water)

Experiment - 23

5 - (2- (2 - Carboxy ethoxy)- 1 - napthyl methylene)- 3 - methyl - 4 - oxo - 2- thioxo thiazolidine.

(mp 152~157°C / recrystallizing solvent: Acetone - Water)

Experiment - 24

5 - (2- (2 - carboxy ethoxy) - 1- napthyl methylone) - 4 - oxo - 2 - thioxo thiazolidine - 3 - Acetic Acid.

(mp 117~123°C / re-crystallizing solvent: Acetic Acid - Water)

Experiment - 25

5 - (5 - bromo - 2 - carboxy methoxy - 6 - methoxy - 1- napthyl methylene) - 4 - oxo - 2 - thiaxo thiazolidine.

Mass spectrum m/Z : 453, 455 (M^+)).

Experiment - 26

5 - (2-carboxy methoxy - 6, 7 - dimethoxy - 1 - napthyl methylene) - 4 - oxo - 2 - thioxo thiazolidine.

(mp 250°C Minimum/recrystallizing solvent: Acctone - Water.

Experiment - 27

5 - (2 - Carboxy methoxy - 6, 7 - dimethoxy - 1 - napthyl methylene) - 3 - methyl - 4 - oxo - 2- thioxo thiazolidine.
(mp 250~255°C / recrystallizing solvent: Acetone - Water)

Experiment - 28

5 - (2-carboxy methoxy - 6, 7 - dimethoxy - 1 - napthyl methylene) - 4- oxo - 2 - thioxo thiazolidine - 3 - Acetic Acid.
(mp 246~248°C / recrystallizing solvent: Actone - Water)

Experiment - 29

5 - (2-(3-Carboxy Propoxy) - 6, 7 - dimethoxy - 1 - napthyl methylene) - 4 - oxo - 2- thioxo thiazolidine.
(mp 201~206°C / re-crystallizing solvent: Acetone - Water)

Experiment - 30

5 - (2 - (3- Carboxy propoxy) - 6, 7 - dimethoxy - 1 - napthyl methylene) - 3 - methyl - 4 - oxo - 2 - thioxo thiazolidine.
(mp 175~180°C / re-crystallizing solvent: Acetone - Water)

Experiment - 31

5 - (2 - (3 - Carboxy propoxy) 6, 7 - dimethoxy - 1- napthyl methylene) - 4 - oxo - 2 - thioxo thiazolidine - 3 - Acetic Acid.
(mp 203~206°C / re-crystallizing solvent: Acetone - Water)

Experiment - 32

5 - (6- bromo - 2 - carboxy methoxy - 1 - napthyl methylene) - 4 - oxo - 2 - thioxo thiazolidine.
(mp 253~257°C / recrystallizing solvent: Acetone - Water)

Experiment - 33

5 - (6 - bromo - 2 - carboxy methoxy - 1 - napthyl methylene) - 3 - methyl - 4 - oxo - 2- thioxo thiazolidine.
(mp 210~215°C / recrystallizing solvent: Acetone - Water)

Experiment 34 :

5-(2-(3-ethoxy carbonyl propoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 255~257°c (Decomposition)/recrystallizing solvent :methanol)

Experiment 35 :

5-(2-(3-carboxy propoxy) benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 250°c minimum/re-crystallizing solvent : Acetic acid-ethanol).

Experiment 36 :

5-(2-(3-carboxy propoxy)benzyledene)-4-oxo-2-thioxothiazolidine.

(mp 237~241°c/re-crystallizing solvent : acetone-water).

Experiment 37 :

5-(2-(3-carboxy propoxy)-5-chlorobenzyledene)-4-oxo-2-thioxo thiazolidine.

(mp 197~203°c/re-crystallizing solvent : Acetone-water)

Experiment 38 :

5-(2-(3-carboxy propoxy)-5-chlorobenzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 157~162°c/re-crystallizing solvent : Acetone-water)

Experiment 39 :

5-(2-(3-carboxy propoxy)-5-chlorobanzyledene)-4-oxo-2-thioxo thiazolidine-3-acetic acid.

(mp 203~206°c/recrystallizing solvent : Acetone-water)

Experiment 40 :

5-(5-bromo-2-(3-carboxy propoxy)benzyledene)-4-oxo-2-thioxo thiazolidine-3-acetic acid.

(mp 212~220°c/recrystallizing solvent: Acetone-water)

Experiment 41 :

5-(5-bromo-2-(3-carboxy propoxy) benzyledene)-3-methyl-4-oxo-2-thioxo thiazolidine.

(mp 167~170°c/recrystallizing solvent: Acetone-water)

Experiment 42 :

5-(5-bromo-2-(3-Carboxy propoxy) benzyledene)-4-oxo-2-thioxothiazolidine.

(mp 209~217°c/re-crystallizing solvent : Acetone-water)

Experiment 43 :

5-(4-(2-carboxy ethoxy) benzyledene)-4-oxo-2-thioxothiazolidine

(mp 244~250°c/recrystallizing solvent : acetone - water.

Experiment 44 :

5-(4-(2-carboxyethoxy) benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 215~219°c (Decomposition)/Recrystallizing solvent : Methanol)

Experiment 45 :

5-(4-(2-carboxyethoxy)benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 241~246°c/recrystallizing solvent : Ethanol-water)

Experiment 46 :

5-(4-(2-carboxyethoxy) benzyledene)-4-oxo-2-thioxothiazolidine-3-propionic acid.

(mp 207~208°c/recrystallizing solvent: Ethanol-water)

Experiment 47 :

5-(4-(2-carboxyethoxy)-3-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 232~236°c/recrystallizing solvent : Ethanol-water)

Experiment 48 :

5-(2-carboxymethoxy-5-chlorobenzyledene)-4-oxo-2-thioxothiazolidine.

(mp 253~255°c/recrystallizing solvent : Acetone-water)

Experiment 49 :

5-(2-carboxymethoxy-5-chlorobenzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 235~240°c/recrystallizing solvent : Acetone-water)

Experiment 50 :

5-(2-carboxy methoxy-5-chlorobenzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 208~212°c/recrystallizing solvent : Acetic acid-water)

Experiment 51 :

5-(5-bromo-2-carboxy methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine)

(mp 239~243°c/recrystallizing solvent : Acetone-water)

Experiment 52 :

5-(5-bromo-2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid)

(mp 200~204°c/recrystallizing solvent : Acetone-water)

Experiment 53 :

5-(4-carboxy methoxy-3-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic mono sodium salt.

(mp 260°c minimum/recrystallizing solvent : Acetic acid-water)

Experiment 54 :

5-(2-carboxy methoxy-3-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid

(mp 250°c minimum/recrystallzing solvent:Acetic acid-water)

Experiment 55 :

5-(2-carboxy methoxy-5-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 208~212°c/recrystallizing solvent:Acetic acid-water)

Experiment 56 :

5-(4-methoxy carbonyl methoxy-3-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 260°c minimum/recrystallizing solvent: Ethanol-water)

Experiment 57 :

5-(4-carboxy methoxy-3-methoxy benzyledene)-4-oxo-2-thioxo-thiazolidine-3-propionic acid.

(mp 213~218°c/recrystallizing solvent :Ethanol-water).

Experiment 58 :

5-(2-carboxy methoxy-3-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-propionic acid.

(mp 212~214°c/recrystallizing solvent : Ethanol-water)

Experiment 59 :

5-(4-carboxy methoxy-3-methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 203~208°c/recrystallizing solvent;Acetic Acid-water)

Experiment 60 :

5-(2-carboxy methoxy-3-methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 163~165°c/recrystallizing solvent : Acetic acid-water)

Experiment 61 :

5-(3-carboxy methoxy-4-methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine mono sodium salt.

(mp 260°c minimum/recrystallizing solvent : Acetic acid-methanol)

Experiment 62 :

5-(3-(3-ethoxy carbonyl-2-propylenyloxy)-4-methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 160~163°c/recrystallizing solvent: Methanol)

Experiment 63 :

5-(2-carboxy methoxy-5-methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 207~212°c/recrystallizing solvent:Acetone-water)

Experiment 64 :

5-(2-carboxy methoxy-5-methoxy benzyledene)-4-oxo-2-thioxothiazolidine.

(mp 224~229°c/recrystallizing solvent: Methanol-water)

Experiment 65 :

5-(3-bromo-4-carboxy methoxy-5-methoxy benzyledene)-4-oxo-2-thioxothiazolidine.

(mp 261~268°c/recrystallizing solvent :Acetone-water)

Experiment 66 :

5-(3-bromo-4-carboxy methoxy-5-methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid

(mp 221~224°c/recrystallzing solvent:Acetone-water)

Experiment 67 :

5-(3-bromo-4-carboxy methoxy-5-methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 217~225°c/recrystallizing solvent:Acetone-water)

Experiment 68 :

5-(4-carboxy methoxy-3-chloro-5-methoxy benzyledene)-4-oxo-2-thiaxothiazolidine-3-acetic acid.

(mp 229~235°c/recrystallizing solvent:Acetone-water)

Experiment 69 :

5-(4-carboxymethoxy-3-chloro-5-methoxy benzyledene)-3-methyl-4-oxo-2-thiaxothiazolidine.

(mp 244~246°c/recrystallizing solvent: Acetic acid-water)

Experiment 70 :

5-(3,5-dibromo-2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid

(mp 241~247°c/recrystallizing solvent: Acetone-water)

Experiment 71 :

5-(3,5-dibromo-2-carboxymethoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 250°c minimum/recrystallizing solvent: Acetone-water)

Experiment 72 :

5-(2-carboxy methoxy-3,5-dichloro benzyledene)-4-oxo-2-thioxothiazolidine.

(mp 255~259°c/recrystallizing solvent : Acetic acid-water)

Experiment 73 :

5-(2-carboxy methoxy-3,5-dichloro benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine.

(mp 233~239°c/recrystallizing solvent:Acetone-water)

Experiment 74 :

5-(2-carboxy methoxy-3, 5-dichloro benzyledene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

(mp 238~243°c/recrystallizing solvent: Acetone-water)

Experiment 75 :

5-(3,5-dibromo-2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine

(mp 250°c minimum/recrystallizing solvent:Acetone-water).

Experiment 76 :

5-(2-carboxy methoxy benzyledene) thiazolidine-2,4-dione

(mp 209~211°c/recrystallizing solvent: Methanol)

Experiment 77 :

5-(2-carboxy methoxy-3-methoxy benzyledene)-thiazolidine-2,4-dione

(mp 230%~ 232°c/recrystallizing solvent: Acetic acid-water)

Experiment 78 :

5-(4-carboxy methoxy-3-methoxy benzyledene) thiazolidine-2,4-dione.

(mp 250°c minimum/recrystallizing solvent: Methanol)

Experiment 79 :

5-(4-carboxy methoxy benzyledene)thiazolidine-2,4-dione

(mp 260~262°c/recrystallizing solvent: Methanol)

Experiment 80 :

5-(2-carboxy methoxy benzyledene) thiazolidine-2,4-dione-3-methyl acetate.

(mp 64~67°c/recrystallizing solvent : Acetone-n-hexane)

Experiment 81 :

5-(4-carboxy methoxy benzyledene)-3-methyl-4-oxo-2-thioxo-thiazolidine

(mp 253~255°c/recrystallzing solvent: Acetic acid-water)

Experiment 82 :

5-(4-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-propionic acid

(mp 236~238°c/recrystallizing solvent: Ethanel-water)

Experiment 83 :

5-(4-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-butyric acid.

(mp 250°c minimum/recrystallizing solvent: Ethanol-water)

Experiment 84 :

5-(4-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-hexanoic acid

(mp 190~193°c/recrystallizing solvent :Ethanol-water)

Experiment 85 :

5-(4-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-undecanoic acid.

(mp 183~187°c/recrystallizing solvent : Ethanol-water)

Experiment 86 :

3-amino-5-(4-carboxy methoxy benzyledene)-4-oxo-2-thioxo-thiazolidine.

(mp 223~226°c/recrystallizing solvent : Ethanol-water)

Experiment 87 :

5-(2-carboxy methoxy benzyledene)-3-methyl-4-oxo-2-thioxothiazolidine

(mp 220~221°c/recrystallizing solvent: Acetic acid-water)

Experiment 88 :

3-amino-5-(2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine.

(mp 203~210°c/recrystallizing solvent : Ethanol-water)

Experiment 89 :

5-(2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-propionic acid

(mp 166~169°c/recrystallizing solvent:Ethanol-water)

Experiment 90 :

5-(2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-butyric acid

(mp 168~172°c/recrystallizing solvent : Ethanol-water)

Experiment 91 :

5-(2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-hexanoic acid.

(mp 176~178°c/recrystallizing solvent : Ethanol-water)

Experiment 92 :

5-(2-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-

3-undecanoic acid.

(mp 137~140°c/recrystallizing solvent : Ethanol-water)

Experiment 93 :

5-(3-carboxy methoxy benzyledene)-4-oxo-2-thioxothiazolidine-3-propionic acid.

(mp 210~212°c/recrystallizing solvent: Ethanol-water)

Experiment 94 :

5-(3-carboxy methoxy benzyledene)-4-oxo-2-thioxo-thiazolidine-3-undecanoic acid.

(mp 145~146°c/recrystallizing solvent : Ethanol-water)

Experiment 95 :

3-amino-5-(3-carboxy methoxy benzyledene)-4-oxo-2-thioxo-thiazolidine.

(mp 240~242°c/recrystallizing solvent: Ethanol-water)

Experiment 96 :

3-benzoylamino-5-(2-carboxy methoxy-5-methoxy benzyledene)-4-oxo-2-thioxothiazolidine

(mp 130~132°c/recrystallizing solvent:Acetone-water)

Experiment 97 :

5-(5-methoxy carbonyl methoxy-2-pyrridylmethylene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

Take the mixture containing 2-methoxy-5-methoxy carbonyl methoxy pyrridine(2.1gms), 4-oxo-2-thioxothiazolidine-3-acetic acid (2.1 gms), sodium acetic anhydrade (1.78 gms) and ice acetic acid (20 ml) and stirr it at 110°c for 48 hours. After the completion of the reaction, eliminate acetic acid under vaccum pressure. Then add dilute hydrochloric acid. Filter the sediment thus obtained. Dissolve it in the mixed solution containing acetic acid-water and carryout the treatment with active carbon. Later re-crystallize it from the mixed solution containing ethanol-water so as to obtain 1.4 gms of 5-(5-methoxy carbonyl methoxy-2-pyridinyl methylene)-4-oxo-2-thioxothiazolidine acetic acid.

Experiment 98 :

5-(5-carboxy methoxy-2-pyrridyl methylene)-4-oxo-2-thioxothiazolidine-3-acetic acid.

Carryout heat reflex in respect of 0.7 gms of 5-(5-methory carbonyl methoxy-2-pyrridyl methylene)-4-oxo-2-thioxo-thiazolidine-3-acetic acid in the mixed solution containing sodium bicarbonate (0.36 gms), water (30 ml) ethanol (80ml) for 2.5 hours. After cooling, eliminate ethanol, add dilute hydrochloric acid. Then filter the sediment thus deposited and carryout recrystallization from acetone-water so as to obtain 0.2 gms of the desired product mp 241~244°c

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